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Digest Paper

Recent advances of desymmetrization protocol applied in natural product total synthesis

Ming Wang [a], Minghao Feng [a], Bingqing Tang [a], Xuefeng Jiang [a,b,*]

[a] Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, PR China
[b] Beijing National Laboratory for Molecular Sciences (BNLMS), Peking University, Beijing 100871, PR China

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ABSTRACT

Desymmetrization synthesis strategy has simplified and improved the efficiency of synthesis, which attracted great attention in the past few decades. Since the strategy has been developed rapidly and got a wide range of applications in natural product total synthesis, the rules are urgent to be summarized. In this Letter, the recent developments of desymmetrization protocol in natural product total synthesis were summarized.

Contents

Introduction

Symmetry is a nature's beauty and implied in the structure of a large number of natural products. The desymmetrization synthesis strategy can afford the desired product easily from the widely available symmetry molecular. As shown in Scheme 1, this strategy has simplified and improved the efficiency of synthesis, which attracted great attention in the past few decades. Since the strategy has been developed rapidly[1] and got a wide range of applications in natural product total synthesis, the rules are urgent to be summarized.

* Corresponding author. Tel./fax: +86 021 5213 3654.
E-mail address: xfjiang@chem.ecnu.edu.cn (X. Jiang).

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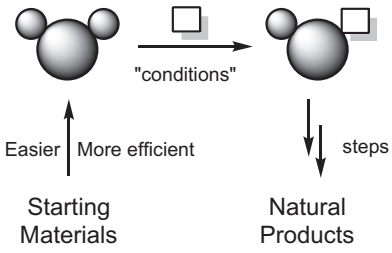
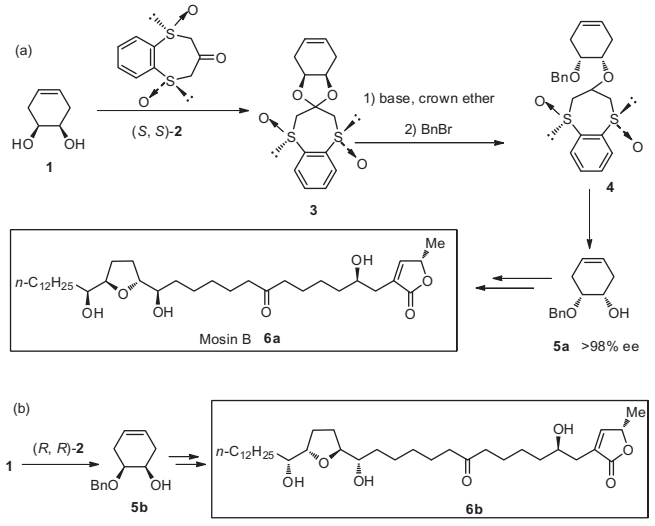


Scheme 1. Overview of desymmetrization strategies for total synthesis.



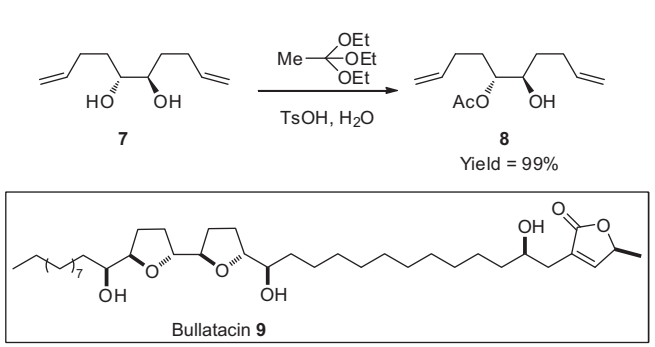
Scheme 2. Desymmetrization of diol **1** by chiral C_2-symmetric bis-sulfoxide.

Here, we summarize the strategy of desymmetrization for natural product total synthesis during the past fifteen years. This review addressed the desymmetrization methods for various symmetry functional groups (including diol, carboxylic ester, α-carbonyl, amine and ether), unsaturated C—C bond, and C_2 symmetric molecular structures in total synthesis. Most of the elegant desymmetrization methods could shorten the synthesis routes dramatically.

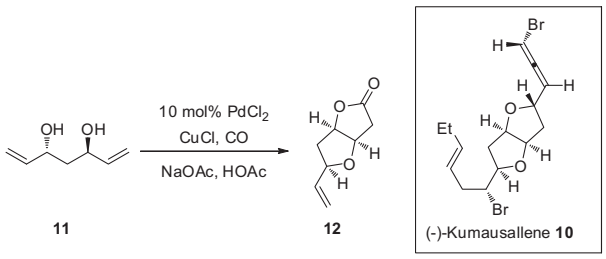
The desymmetrization of symmetry functional group

Diol

The desymmetrization of diols is a most common desymmetrization strategy in total synthesis which includes chemical catalysis and enzymatic catalysis.



Scheme 3. Desymmetrization of diol **7** by triethyl orthoacetate.



Scheme 4. Desymmetrization of C_2-symmetric diol **11**.

Chemical catalysis

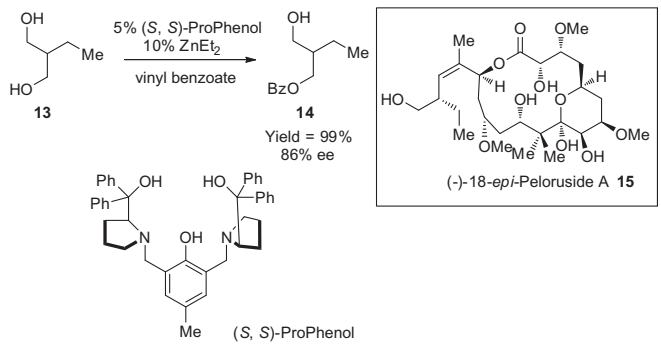
Mosin B was isolated by McLaughlin and co-workers from the bark of *Annona squamosa* in 1997. As a mono-tetrahydrofuran acetogenin, it has selective and potent cytotoxic activity against the human pancreatic tumor cell line.[2a]

In 2001, Tanaka group[2b] reported the first total synthesis of Mosin B **6a** in 20 steps from desymmetrized alcohol **5a** and overall yield was 1.1%. This work was accomplished by using asymmetric desymmetrization of the σ-symmetric diol **1** as one of key steps. They used C_2-symmetric bis-sulfoxide (*S*,*S*)-**2** as a chiral auxiliary, which developed by themselves[2b], and acetalization of *meso*-diol **1** gave product **3**. Base-promoted diastereoselective acetal fission of **3** followed by *O*-benzyl protected of the resulting alkoxide to prevent recyclization afforded **4**. After removing the chiral auxiliary, **5a** can be obtained in 98% ee (Scheme 2a). The unnatural diastereomer **6b** also can be synthesized from **5b** using (*R*,*R*)-**2** as a chiral auxiliary by the same procedure (Scheme 2b). They suggested that natural mosin B is **6a**, not **6b** by these synthetic results. Antiproliferative effects of **6a** and **6b** were also investigated in their subsequent work.[2c]

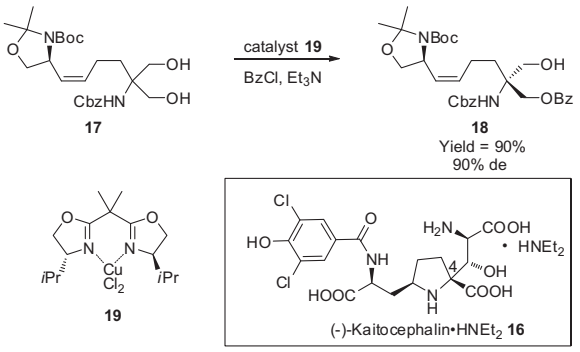
In 2006, Pagenkopf group reported the total synthesis of Bullatacin **9** that was isolated from the tropical plant family *Annonaceae*.[3] The desymmetrization of **7** was accomplished by using triethyl orthoacetate as the acetylation reagent to give monoacetate **8**. **8** is a critical intermediate for the synthesis of bis(THF) core segment (Scheme 3).

(−)-Kumausallene **10**, is one member of the nonisoprenoid sesquiterpenes family and was isolated from the marine red alga *Laurencia* by Kurosawa group in 1983.[4] Tang and co-workers developed enantioselective total synthesis of (−)-Kumausallene **10** through a desymmetrization strategy for the construction of the 2,5-*cis*-substituted THF ring.[5] Their synthesis began with the readily prepared C_2-symmetric diol **11** (96% ee). The palladium-catalyzed cascade reaction of **11** provided bicyclic lactone **12** in good yield as a single stereoisomer. Having the bicyclic lactone **12** in hand, they accomplished the assembly of (−)-Kumausallene **10** in eight steps from **12** (Scheme 4).

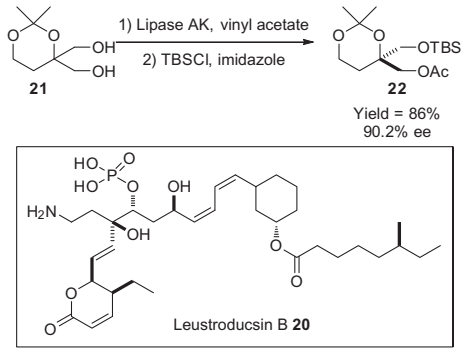
As a macrolide natural product, Peloruside A was isolated from a marine sponge *Mycale hentscheli*, which shows antimitotic



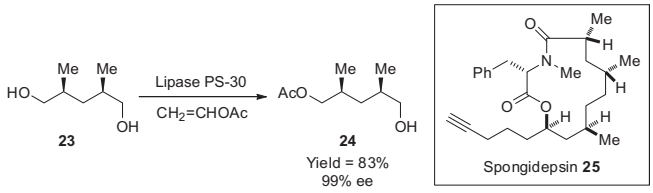
Scheme 5. Desymmetrization of diol **13** by dinuclear zinc asymmetric catalyst.



Scheme 6. Desymmetrization of diol **17** by dinuclear copper asymmetric catalyst.

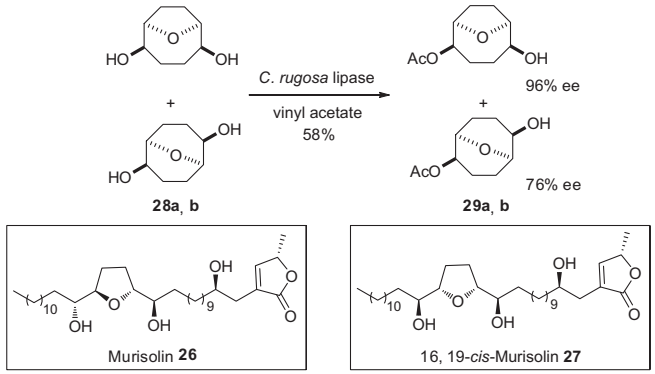


Scheme 7. Desymmetrization of diol **21** with Lipase AK and vinyl acetate.



Scheme 8. Desymmetrization of diol **23** with Lipase PS-30 and vinyl acetate.

activity.[6] In 2013, Trost group developed the total synthesis of (−)-18-*epi*-Peloruside A **15** using an alkyne linchpin strategy.[7] In their synthetic route, the desymmetrization of *meso*-1,3-diol **13** was completed by using a dinuclear zinc asymmetric catalyst previously developed in their laboratory.[8] Enantioenriched monobenzoylated product **14** (86% ee) can be obtained when using catalytic diethylzinc and (*S*,*S*)-ProPhenol (Scheme 5).



Scheme 9. Desymmetrization of diol **28a**, **b** for the total synthesis of Murisolin.

(−)-Kaitocephalin **16** was isolated from the filamentous fungus *Eupenicillium shearii* PF1191 by Shin-ya et al. in 1997.[9] In 2013, Kang group established their synthesis of (−)-Kaitocephalin with the C4 quaternary carbon was installed by the desymmetrization.[10] When diol **17** was subjected to benzoylation conditions using the chiral catalyst **19**, the monobenzoate **18** was obtained in 90% yield with 90% de, which was subsequently converted to the Kaitocephalin diethylamine salt by multi-steps (Scheme 6).

Enzyme catalysis

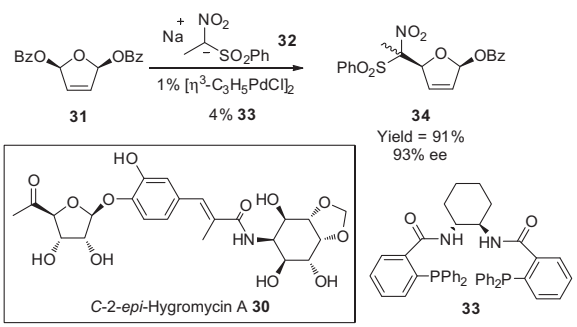
Leustroducsin B **20** is a mono-tetrahydrofuran acetogenin, isolated by Kohama et al. from the culture broth of *Streptomyces platensis* SANK 60191 and shows a variety of biological activities and is likely to be developed as a new drug candidate.[11] In 2003, Fukuyama group reported the first total synthesis of Leustroducsin B **20**, in which lipase-mediated enzymatic desymmetrization of the *meso*-diol **21** was a key step.[12] At first, desymmetrization of *meso*-diol **21** with Lipase AK and vinyl acetate furnished the optically active acetate, and then the monoacetate was immediately protected as its TBS ether **22**.[13] The optically active **22** was determined to be 90.2% ee (Scheme 7).

In 2004, Ghosh group employed the enzymatic desymmetrization of **23** with lipase PS-30 to provide the monoacetate **24** in 99% ee. The monoacetate**24** was an effective starting material for their enantioselective synthesis of important segments that lead to the total synthesis of (−)-Spongidepsin **25**.[14] Spongidepsin, as the novel cyclodepsipeptide, displayed potent cytotoxicity against a variety of cancer cell lines, was isolated from the Vanuatu marine sponge *Spongia* sp. by Riccio group[15a] and was assigned by Forsyth group (Scheme 8).[15b]

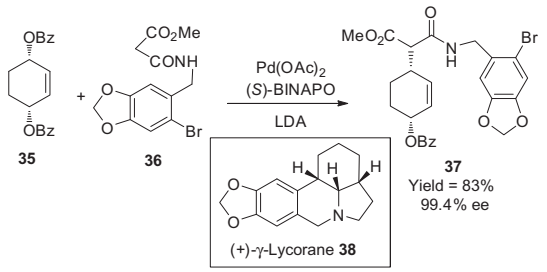
Murisolin **26** and 16,19-*cis*-Murisolin **27**, which belong to the murisolin class of monotetrahydrofuran acetogenins, were discovered by Cole group[16a] in 1982 and shows high cytotoxicity which rivals that of taxol.[16b] In 2012, Haufe group developed a novel Lego-like building block strategy toward the total synthesis of **26** and **27** in 1.6% or 0.2% overall yields.[17] In their strategy, desymmetrization of inseparable diols **28a**, **b** mixture, gave a 62:38 mixture of intermediates **29a** (96% ee) and **29b** (76% ee) by using *Candida rugosa* lipase and vinyl acetate (Scheme 9).

Carboxylic esters and anhydrides

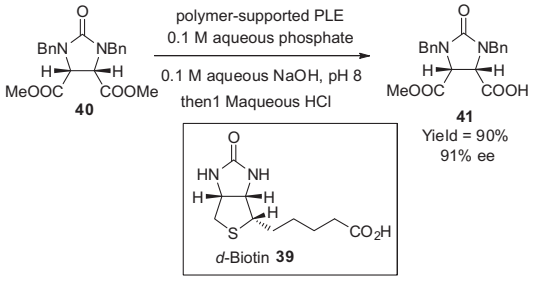
In 2001, Trost group[18] reported the synthesis of the furanoside moiety of the *C*-2 epimer of Hygromycin A **30** which is the analogue of natural product Hygromycin.[19] In order to synthesize the furanoside part of *C*-2-*epi*-Hygromycin A **30**, they used the sodium salt of 1-phenylsulfonyl-1-nitroethane **32** to desymmetrize of bisbenzoate **31**. They found that using 4% of ligand **33** with 1%[{η^3-C_3H_5PdCl}$_2$] afforded the monobenzoate **34** in 93% ee. It should be noted that they chose **32** as an acetyl equivalent because



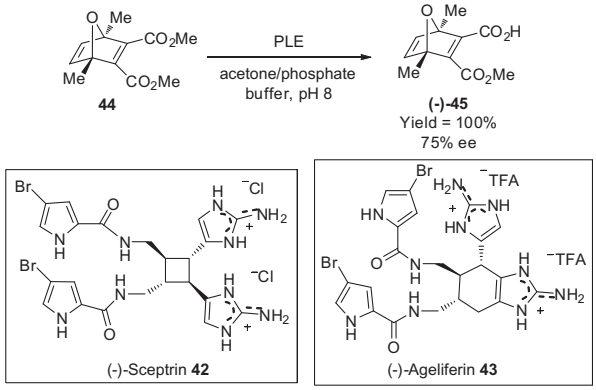
Scheme 10. Desymmetrization of bisbenzoate **31**.



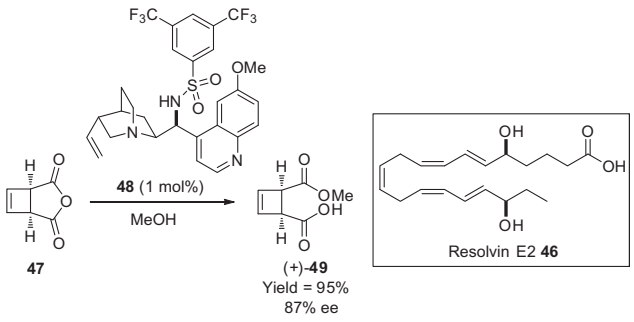
Scheme 11. Desymmetrization of *meso*-1,4-dibenzoyloxycyclohex-2-ene **35**.



Scheme 12. Desymmetrization of *meso*-dicarboxylic diesters **40**.



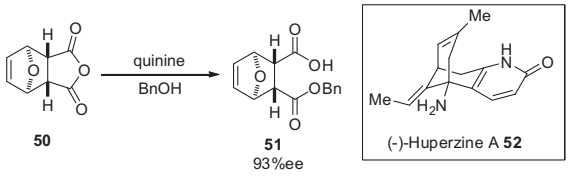
Scheme 13. Desymmetrization of *meso*-diester **44**.



Scheme 14. Desymmetrization of *meso*-anhydride **47**.

of its soft nucleophilicity and the lack of acidic protons after alkylation (Scheme 10).

In 2006, Ojima group developed a highly efficient Pd/phosphoramidite ligand-catalyzed asymmetric allylic alkylation. They employed this method for desymmetrization of *meso*-1,4-dibenzoyloxycyclohex-2-ene **35** to afford **37** with 99.4% ee. From **37**, they only needed five steps to synthesize the natural product



Scheme 15. Desymmetrization of anhydride **50**.

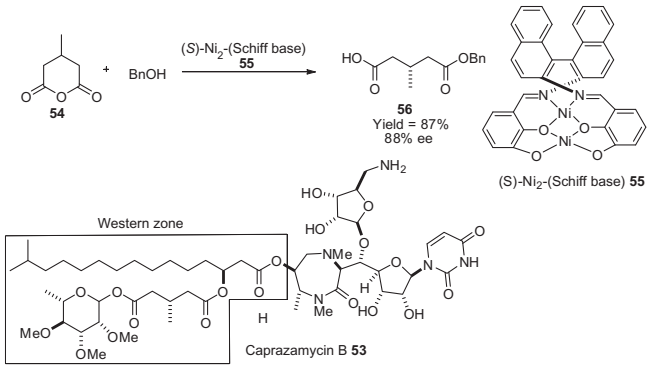
(+)-γ-Lycorane **38**, which was isolated from the plants of Amaryllidacae family and has attracted much attention for its total synthesis (Scheme 11).[20]

Biotin **39** is one of the water-soluble B vitamins. It was isolated from egg yolk by Kogl in 1936.[21a] Later du Vigneaud et al. isolated it from beef liver and milk concentrates in 1941.[21b] Although marked advances in the total synthesis of *d*-Biotin have been achieved,[21c] Chen group developed another new and practical strategy in 2005.[22] One of crucial steps of their approach was asymmetric enzymatic desymmetrization of *meso*-dicarboxylic diester **40**. They used immobilized PLE (pig liver esterase) on Eupergit C as the catalyst and conducted the reaction in buffer which was kept constant at pH 8. The hemiester **41** was obtained with 91% ee and the ee value can be upgraded to 98.5% by recrystallization (Scheme 12).

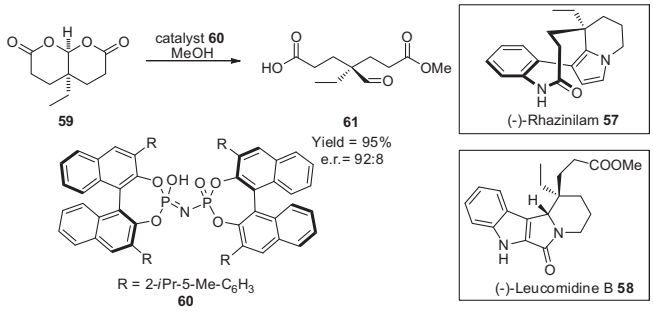
As the marine-derived dimeric pyrrole-imidazole alkaloids, Sceptrin **42** and Ageliferin **43** have a range of useful bioactivities.[23] The racemic form of **42** and **43** has been synthesized by some groups.[24] Baran group reported the first asymmetric synthesis of both enantiomers of Sceptrin **42** and Ageliferin **43** in 2006.[25] Their synthesis commenced with the enzymatic desymmetrization of *meso*-diester **44** using PLE in buffer and pH 8 to provide monoester (−)-**45** in 75% ee. Subsequently, they accomplished the total synthesis of sceptrin **42** and ageliferin **43** with high overall yield (Scheme 13).

Resolvin E2 **46** shows potent anti-inflammatory properties in murine peritonitis.[26] Inoue group reported the total synthesis of Resolvin E2 **46** by enantioselective desymmetrization of achiral *meso*-anhydride **47**.[27] With treatment of **47** with 1 mol% of **48** in methanol, they obtained (+)-**49** with 87% ee. Subsequently, the important fragment synthesized from (+)-**49** was assembled into Resolvin E2 **46** easily (Scheme 14).

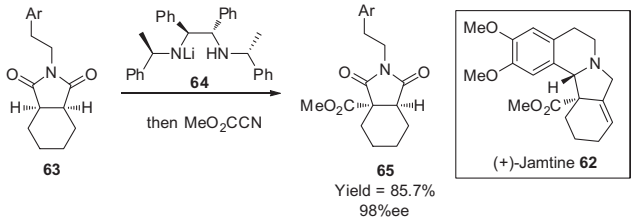
In 2009, Fukuyama group utilized the desymmetrization of anhydride **50** to assemble the natural product (−)-Huperzine A **52**,[28] which was isolated from *Huperzia serrata* by Liu et al. in 1986 and exhibits a potent inhibitory activity against acetylcholinesterase.[29] Their total synthesis commenced with the desymmetrization of anhydride **50** which was treated with quinine and benzyl alcohol to give carboxylic acid **51** with 93% ee. They obtained a crit-



Scheme 16. Desymmetrization of anhydride **54**.



Scheme 17. Desymmetrization of bicyclic bislactone **59**.



Scheme 18. Desymmetrization of *meso*-imide **63**.

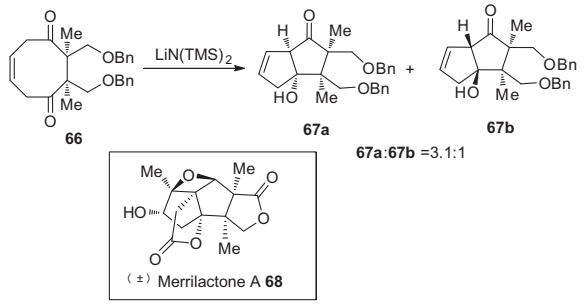
ical intermediate from **51** that lead to the synthesis of (−)-Huperzine A **52** (Scheme 15).

Caprazamycin B **53**, a novel lipo-nucleoside antibiotic, was isolated from the culture broth of the actinomycete strain *Streptomyces* sp. MK730-62F2 and shows excellent antimycobacterial activity in vitro against drug-susceptible and multidrug-resistant *Mycobacterium tuberculosis* strains. A simple and convenient synthesis of the western zone of Caprazamycin B using desymmetrization as one of the key elements was reported by Shibasaki and co-workers[30] In the presence of (*S*)-Ni$_2$-(Schiff base) **55** complex, 3-methylglutaric anhydride **54** was treated with BnOH to give the corresponding chiral hemieste **56** in 87% yield with 88% ee (Scheme 16).

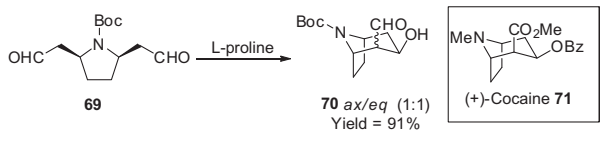
Very recently, Zhu and co-workers established their synthetic route of (−)-Rhazinilam **57** and (−)-Leucomidine **58**,[31] highlighting the desymmertrization of bislactone **59** as the key step. Different kinds of chiral phosphoric acids derived from (*S*)-BINOL and (*S*)-SPINOL were explored in various solvents at −60 °C to room temperature. Finally, the optimized conditions were settled down as that using the catalyst **60** to promote the transformation in 1,4-dioxane at room temperature, which gave the desired product **61** in 95% yield with 92:8 e.r. (Scheme 17).

α-Carbonyl

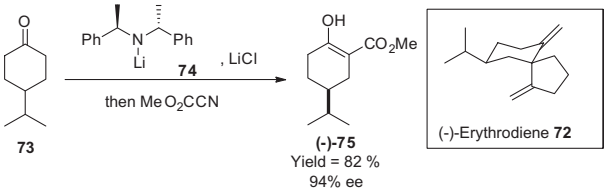
Simpkins group developed chiral lithium amide bases (e.g., **64**) catalyzed highly enantioselective desymmetrization of dicarbonyl



Scheme 19. Desymmetrization of *meso*-diketone **66**.



Scheme 20. Desymmetrization of *meso*-dialdehyde **69**.



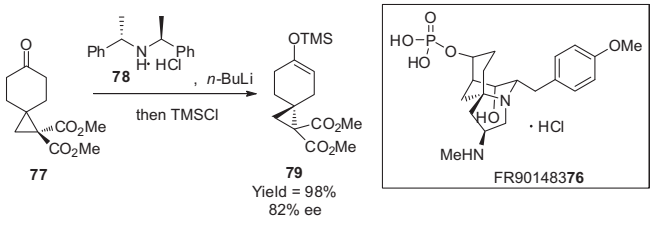
Scheme 21. Desymmetrization of 4-isopropylcyclohexanone **73**.

derivatives. In 2003, their group[32] employed the strategy for asymmetric total synthesis of medicinal alkaloid (+)-Jamtine **62** which was reported, in the form of an *N*-oxide, as one of the small group of isoquinoline alkaloids isolated from the climbing shrub *Cocculus hirsutus*.[33] In their route, desymmetrization of *meso*-imide **63** was accomplished by employing a monolithiated diamine base **64**. The carboxymethylation product (−)-**65** was obtained with 98% ee. Subsequently, they finished the synthesis of (+)-Jamtine **62** in 4 steps from (−)-**65** (Scheme 18).

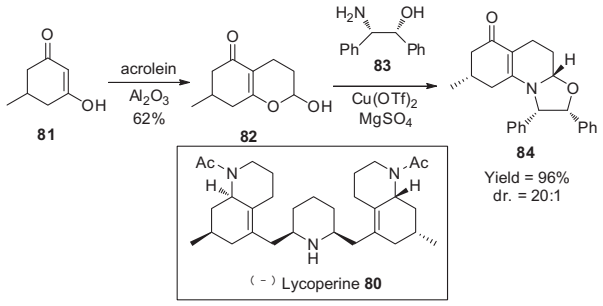
Hirama and co-workers reported desymmetrization of *meso*-diketone **66** through an intramolecular aldol reaction in 2003.[34] In their desymmetrization protocol, treatment of **66** with LiN(TMS)$_2$ in THF at −100 °C lead to the selective formation of desired product **67a** as the major product. Employing the reaction as one of key steps, they accomplished the total synthesis of natural product (±)-Merrilactone A **68**, which was isolated from *Illicium merrillianum* in 2000, has been shown to possess neurotrophic activity (Scheme 19).[35]

Cocaine was isolated from a variety of plant sources (e.g., *Hyoscyamus niger*, *Atropa belladonna*), has a long and important history in medicine.[36] In 2004, Pearson group utilized intramolecular aldol reaction to achieve the desymmetrization of *meso*-dialdehyde **69** for the total synthesis of (+)-Cocaine **71**.[37] Using the conditions reported by List, the L-proline catalyzed aldol reaction afforded products **70** ax/eq as a 1:1 mixture. They synthesized the natural product (+)-Cocaine **71** in three steps from the **70** ax/eq mixture (Scheme 20).

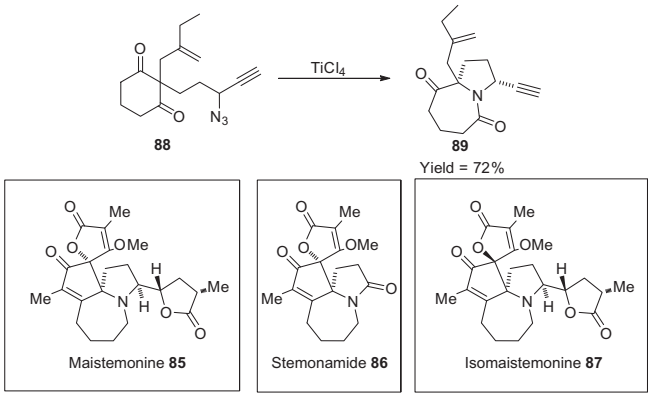
In 2005, Renaud group[38] developed a radical spirocyclization approach to a short and efficient synthesis of (−)-Erythrodiene **72** which was isolated from Caribbean gorgonian octocoral *Erythropodium caribaeorum*.[39] They utilized desymmetrization of 4-isopropylcyclohexanone **73** to obtain the key optically pure segment (−)-**75**. As shown in Scheme 21, deprotonation of **73** with lithium *N*,*N*-bis[(*R*)-1-phenylethyl]amide (**74**) and reaction with methylcyanocarbonate afforded the β-keto ester (−)-**75** in 94% ee.



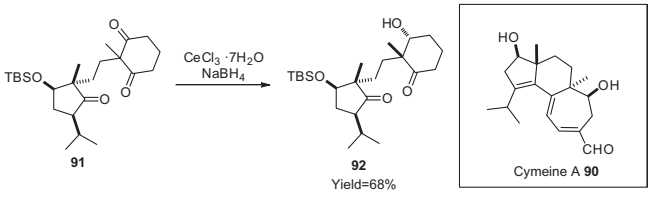
Scheme 22. Desymmetrization of prochiral spirofused **77**.



Scheme 23. Desymmetrization of hemiacetal **81**.



Scheme 24. Desymmetrization of **88** via an Schmidt reaction.



Scheme 25. Desymmetrization of triketone **91**.

Immunosupressant FR901483 **76**, a potent immunosuppressive alkaloid, was isolated from the fermentation broth of *Cladobotryum* sp. and shows biological activity.[40] In 2009, Kerr and co-workers reported the enantioselective total synthesis of FR901483 **76**.[41] The first step was desymmetrization of prochiral spirofused **47**. Enol ether **79** was prepared in 82% ee by treating ketone **77** with the chiral lithium amide derived from **78** in the presence of chlorotrimethylsilane. Subsequently, FR901483 **76** was synthesized smoothly from **79** (Scheme 22).

Lycoperine A **80**, exhibited a moderate inhibitory activity against acetylcholine esterase from bovine erythrocyte, was isolated from the club moss *Lycopodium hamiltonii* by Kobayashi and co-workers in 2006.[42] Rychnovsky group described the total synthesis of Lycoperine A **80** through a highly convergent route which commenced with commercially available diketone **81**.[43] Diketone **81** was combined with acrolein to afford hemiacetal **82** which was an acyclic version of the underlying symmetric dione. Desymmetrization of **82** by condensation with amino alcohol auxiliaries led to the formation of vinylogous amides **84** in 20:1 dr. The important segment octahydroquinoline was prepared from **84** straightforwardly (Scheme 23).

The *Stemona* alkaloids, a class of polycyclic alkaloids, have been isolated to date from the monocotyledonous family Stemonaceae.[44] In 2011, Tu and co-workers presented a full account of the total synthesis of (±)-Maistemonine **85**, (±)-Stemonamide **86**, and (±)-Isomaistemonine **87**.[45] In their route, one of the highlighted steps was an intramolecular Schmidt reaction of **88** under $TiCl_4$ catalyzed conditions, which afforded a desymmetrizing product **89** in the form of a single diastereoisomer (Scheme 24).

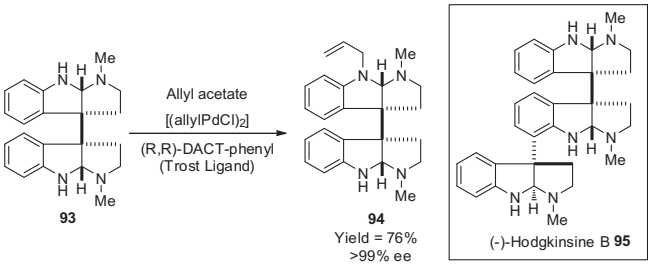
Cyrneine A **90**, featuring a tricyclic 5–6–7 ring system containing a hexatrienal unit, which enhances neurite outgrowth in pheochromocytoma cells,[46] was firstly total synthesized by Gademann and co-workers in 2012.[47] A remarkable diastereoselective reduction of the triketone **91** under Luche conditions resulted in high regioselectivity, and the 5*R*,6*R* diastereoisomer **92** was obtained as the major product in a ratio of 4.25:1, with none of the unlike diastereoisomers observed. The obtained selectivity could be explained by the steric hindrance of the substrate and the use of Luche reagents (Scheme 25).

Amine

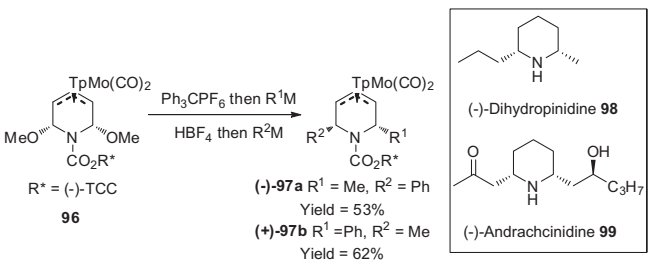
In contrast to catalytic asymmetric desymmetrization of *meso*-diol, the desymmetrization of diamine was less reported. In 2011, Willis and co-workers reported[48] the desymmetrization of *meso*-chimonanthine **93** for the total synthesis of natural product Hodgkinsine B **95** which was isolated from Amazon *Psychotria* species.[49] They achieved enantioselective *N*-monoallylation of *meso*-diamine **93** with a (allyl-Pd—Cl)$_2$/Trost ligand catalyst which are the desymmetrization conditions of Taguchi and co-workers,[50] to afford monoallyl product **94** in >99% ee. This strategy was significant for completing their total synthesis (Scheme 26).

Ether

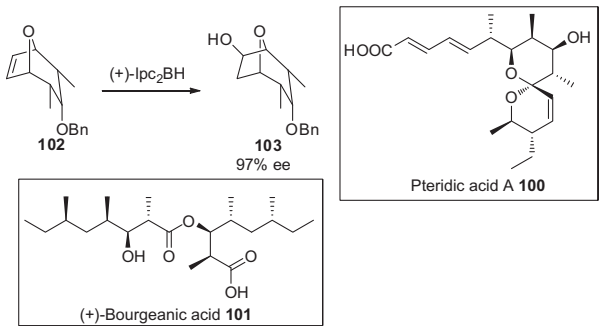
The desymmetrization of diether was less reported too. Liebeskind group developed a highly diastereoselective methoxide abstraction method which relies on the 'desymmetrization' imparted by the chiral *N*-protecting group ($-CO_2R^*$ in **96**.[51] As shown in Scheme 27, the 2,6-disubstituted dihydropyridinylmolybdenum complex (−)-**97a** was provided by methoxide abstraction of (−)-**96** with Ph_3CPF_6, subsequent addition of MeMgBr, then ionization of the other methoxide with HBF_4, and addition of PhMgBr. When reversing the order of nucleophiles added



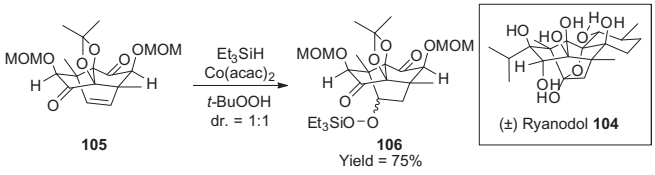
Scheme 26. Desymmetrization of *meso*-chimonanthine **93**.



Scheme 27. Desymmetrization of diether by methoxide abstraction.



Scheme 28. Desymmetrization of bicyclic olefin **102**.



Scheme 29. Desymmetrization of **105**.

(PhMgBr then MeMgBr), they can obtain the other diastereomeric (+)-**97b**. With the two products in hand, they synthesized the (−)-Dihydropinidine **98** and (−)-Andrachcinidine **99** (an alkaloid isolated from *Andrachne aspera*[52]) straightforwardly.

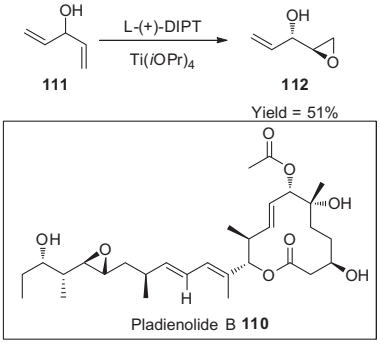
The desymmetrization of unsaturated C—C bond

Monoenes

The desymmetrization of unsaturated C—C bonds (including monoenes and dienes) via hydroxylation or dihydroxylation was also developed in total synthesis.

Pteridic acid A **100**, a spirocyclic polyketide natural product, having potent plant growth regulator activity, was isolated by Igarashi and co-workers in 2002 from the fermentation broth of *Streptomyces hygroscopicus* TP-A0451.[53a] (+)-Bourgeanic acid **101** was isolated by Bodo et al. in 1973 from the species of lichen Ramalina.[53b] Yadav group utilized the desymmetrization of bicyclic olefin with Brown's chiral hydroboration (lpc$_2$BH) to start the total synthesis of natural products **100** and **101**.[54] As shown in Scheme 28, hydroxylation of bicyclic olefin **67** with (+)-lpc$_2$BH afforded the chiral bicyclic alcohol **103** in 97% ee, leading to the total synthesis of Pteridic acid A **100**. When using the (−)-lpc$_2$BH as the catalysis for the hydroxylation of **102** to afford the enantiomer of **103**, they accomplished the total synthesis of (+)-Bourgeanic acid **101**.

Recently, Inoue group described a newly designed route for the total synthesis of Ryanodol **104**,[55] a derivative of natural product Ryanodine, has different biological activities with the other Ryanoid derivatives.[56] The first necessitated step of their strategy was desymmetrization of C_2-symmetric intermediate **105**. Because of the strong tendency of the newly generated alcohol to cyclize into the unreactive hemiacetal, they needed to protect the newly generated alcohol immediately. Their approach is shown in Scheme 29, **105** was subjected to Et_3SiH with 20 mol % of $Co(acac)_2$ and 5 mol % *t*-BuOOH under an oxygen atmosphere to afford Et_3Si-peroxide **106**. This step provided a critical foundation for their total synthesis of Ryanodol **104** in 22 steps.

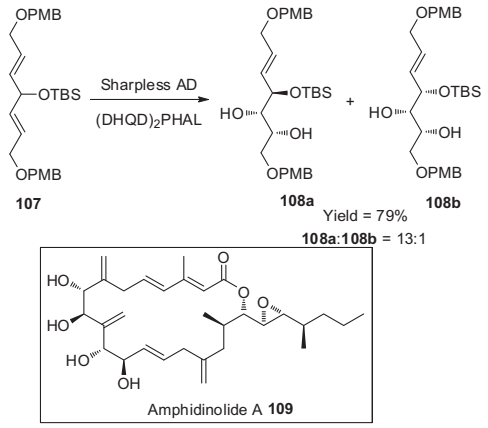


Scheme 31. Desymmetrization of divinyl carbinol **111**.

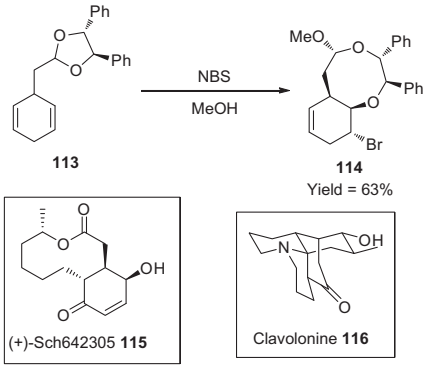
Dienes

The desymmetrization of dienes also was involved in the total synthesis. Trost group described Sharpless AD/(DHQD)$_2$PHAL-catalyzed asymmetric Sharpless dihydroxylation of diene substrate **107** to afford the diols **108a** and **108b** as a 13:1 mixture with 90% ee.[57] Using this strategy, they completed the total synthesis of marine product Amphidinolide A **109** which was isolated from dinoflagellate Amphidinium by Kobayashi group in 1986 (Scheme 30).[58]

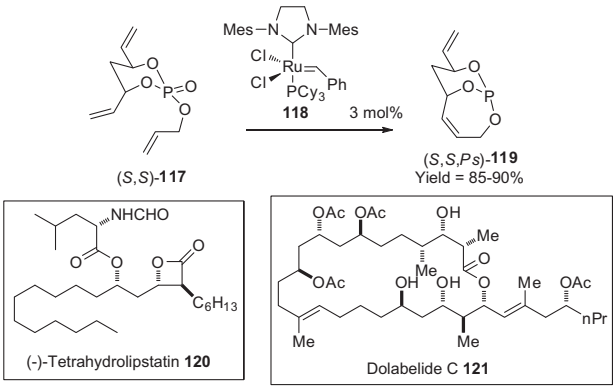
Pladienolide B **110** was capable of inhibiting the proliferation of human cancer cells, which was isolated from a *Streptomyces platensis* (Mer-11107) by Sakai et al. in 2004.[59] Ghosh group reported enantioselective total synthesis of Pladienolide B **110** by employing asymmetric desymmetrization of commercially available divinyl carbinol **111** as the first step.[60] Asymmetric Sharpless epoxidation of **111** afforded the corresponding epoxide **112** as a single isomer.



Scheme 30. Desymmetrization of diene **107**.



Scheme 32. Desymmetrization of cyclohexadiene acetal **113**.



Scheme 33. Desymmetrization of triene (*S*,*S*)-**117**.

Intermediate **112** can be used to synthesize the important segment for the assembly of Pladienolide B **110** (Scheme 31).

(+)-Sch 642305 **115** was first isolated from *Penicillium Verrucosum* by Chu and co-workers in 2003 and shows to be a potent inhibitor of bacterial.[61] In 2007, Fujioka group developed a concise asymmetric synthesis of (+)-Sch 642305 **115** by chiral auxiliary multiuse methodology.[62a] They employed cyclohexadiene acetal **113** as the starting material since the chiral nonracemic hydrobenzoin in this material can be used as chiral auxiliary for desymmetrization of itself diene. As shown in Scheme 32, bromo acetal **114** was obtained by intramolecular bromoetherification to complete desymmetrization of cyclohexadiene acetal **113**. Intermediate **114** was a critical material for subsequent reaction that led to the synthesis of (+)-Sch 642305 **115**. Employing the same methodology, they synthesized the natural product Clavolonine **116**[62b] which was isolated from the clubmoss *Lycopodium clavatum* by Burnell and Taylor in 1960.[63]

(−)-Tetrahydrolipstatin **120** is an antiobesity drug marketed and exhibits selective inhibition of thioesterase activity of fatty acid synthase in cancer cells.[64] In 2010, Hanson group reported a concise total synthesis of (−)-Tetrahydrolipstatin **120** in nine steps from the readily prepared material.[65a] They synthesized the bicyclic phosphate (*S*,*S*,P_S)-**119** via RCM desymmetrization of triene (*S*,*S*)-**117** using Grubbs' catalyst **118**. With intermediate (*S*,*S*,P_S)-**119** in hand, the subsequent steps are unobstructed to complete the total synthesis of (−)-Tetrahydrolipstatin **120**. Using the same desymmetrization strategy, they accomplished the total synthesis of another natural product Dolabelide C **121**,[65b] which was isolated from the sea hare *Dolabella auricularia* in 1997 and exhibited cytotoxicity against HeLa-S3 cells (Scheme 33).[66]

Conclusions

In short, we have summarized the recent developments of desymmetrization protocol in natural product total synthesis. As shown in this digest, many efficient desymmetrization strategies have been employed in total synthesis. With the development of desymmetrization protocol in organic chemistry, we believe more and more desymmetrization methods will be applied in total synthesis. In the meanwhile, the exploitation of novel desymmetrization strategies in total synthesis is necessary as well.

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